

*Original Article*

## **Reversible acute renal failure from gross haematuria due to glomerulonephritis: not only in IgA nephropathy and not associated with intratubular obstruction**

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**Abstract.** Seven patients with acute renal failure due to gross haematuria caused by glomerulonephritis are described. Gross haematuria lasting 4–40 days led to acute impairment of renal function of variable severity (peak plasma creatinine 1.3–12 mg/dl) and duration. While partial recovery of renal function occurred in all patients within few days, complete remission was observed only some months later. Three patients had IgA nephropathy (2 the primary form and 1 nephritis secondary to Schönlein–Henoch purpura), two patients had acute postinfectious glomerulonephritis, and two others had focal necrotizing (pauci-immune) glomerulonephritis. The glomerular changes seen in the renal biopsy were not enough to explain *per se* the renal function impairment. Tubular changes, however, were severe and consisted of tubular necrosis, erythrocyte casts, erythrocyte phagocytosis by tubular cells, accompanied by interstitial damage (oedema, red-cell extravasation, and inflammatory infiltrates). Study of the renal biopsies by immunofluorescence revealed no retrodiffusion of Tamm–Horsfall protein into the glomerular Bowman's space, a sign of obstructed tubular flow in any case. It is concluded that acute renal failure due to gross haematuria in glomerulonephritic patients may not occur only in IgA nephropathy, as reported so far, and is not associated with intratubular obstruction.

**Key words:** acute renal failure; acute tubular necrosis; glomerulonephritis; gross haematuria; Tamm–Horsfall protein

### **Introduction**

Reversible acute renal failure (ARF) due to gross haematuria in a patient with glomerulonephritis was

first described in 1983 by Kincaid-Smith *et al.* [1]. Since then about 40 similar cases have been reported [2–7], all but one with IgA nephropathy [8]. The cause of ARF in this condition is not yet clear, but it has been hypothesized that it might be due to either intratubular obstruction by erythrocyte casts [1,9] or to a tubulotoxic effect of erythrocyte-derived substances [1,3].

The aims of this study were (1) to describe our experience with ARF due to gross haematuria in glomerulonephritic patients; (2) to evaluate the role of intratubular obstruction in the pathogenesis of the renal dysfunction.

### **Subjects and methods**

#### *Inclusion criteria*

The patients included in the study had abrupt renal function impairment (i.e. plasma creatinine increased to at least 50% above the basal value, when available) and typical tubular changes in the renal biopsy (i.e. tubular necrosis, variable amounts of erythrocyte casts, erythrocyte phagocytosis by tubular cells) in the absence of glomerular lesions that could *per se* explain the acute renal failure.

#### *Clinical parameters*

Sex, age of the patients, and plasma creatinine (basal, peak, and at discharge from hospital) in mg/dl; duration of the episode of gross haematuria, and the time required to obtain full recovery from the ARF.

#### *Pathology*

For light-microscopy 4- $\mu$ m sections were obtained from a renal biopsy and stained by H&E, PAS, trichrome (AFOG), silver methenamine, and Perl's Prussian blue method for haemosiderin. Semiquantitative evaluation was done by one of us (IE), based on the parameters reported in Table 2. The severity of the lesions was scored from 0 to + + +. Acute tubular necrosis (ATN) was classified according to Solez

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*et al.* [10] and semiquantitatively evaluated by summing the following: intratubular necrotic cells, denuded areas of tubular basement membrane, ruptured tubular basement membranes, and loss of brush border in proximal tubules, all scored from 0 to 3. When there was enough tissue, electron-microscopy was also performed by one of us (MJM), according to standard procedures. Immunofluorescence was performed by one of us (FGB) on paraffin sections, as reported elsewhere [11]. Sections were stained with fluoresceinated antisera to IgA, IgG, IgM, C1q, C3 and fibrin (ogen) (Dakopatts, Glostrup, Denmark).

To study intratubular obstruction, biopsy kidney sections were stained with a polyclonal monospecific fluoresceinated sheep anti-human serum to Tamm-Horsfall protein (THp) (Human Uromucoid FITC, The Binding Site, Birmingham Research Park, Birmingham, UK, B15 2SQ), diluted in phosphate-buffered saline (PBS) 1:10. A sign of intratubular obstruction was considered the presence of THp within Bowman's capsule [12–18]. Stain intensity was scored from 0 to + + +. As controls we used 159 renal biopsies from patients with different renal diseases, in 24 of which THp retrodiffusion into the glomerular Bowman's space was found (focal distribution in 19, diffuse in 5, stain intensity ranging from + + to + + +) [19]. In both negative and positive controls THp was constantly observed in the cytoplasm of the distal tubular segments (intensity of stain + to + +), and in the intratubular casts (intensity of stain + + to + + +), which is a usual finding in renal biopsies [20].

Due to the small number of patients, no statistical inferential analysis was attempted.

## Results

Seven patients, submitted to renal biopsy from September 1988 to January 1994, fit the inclusion criteria (Table 1). One patient (number 2) has already been described in detail elsewhere [8]. All were men, with ages ranging from 16 to 85 years (mean  $\pm$  SD,  $50.8 \pm 23.5$ ). The duration of gross haematuria ranged from 4 to 40 days (mean  $\pm$  SD:  $22.2 \pm 13$ ).

Non-nephrotic proteinuria was present in six patients. Plasma creatinine was normal in the six patients for whom it was available before the appearance of gross haematuria. Peak plasma creatinine ranged from 1.3 to 12 mg/dl (mean  $\pm$  SD,  $6.5 \pm 3.8$ ). Patient 2 required two haemodialysis sessions before renal function started to recover. Rapid and partial

recovery of renal function was seen in all patients, as shown by the levels of plasma creatinine at discharge. In four patients this occurred spontaneously while three of the four patients with necrotizing lesions in the renal biopsy (patients 2, 4, and 7) had been given three (nos 4 and 7) or four (no. 2) i.v. methylprednisolone pulses (0.5 g each) followed by oral prednisone 0.5 mg/kg (for 3 weeks in patient 2, 8 weeks in patient 4, 12 weeks in patient 7). In patients 1 to 6 full recovery of renal function occurred over periods ranging from 58 days to 11 months. Patient 1, however, had further episodes of gross haematuria in the months following the discharge. For patient 7, renal function was not normal at the last check (plasma creatinine = 2.5 mg/dl), 60 days after peak plasma creatine level. The patient, however, is still under observation at present. There was some correlation between the duration of gross haematuria and the peak plasma creatinine levels, but with striking exceptions, as demonstrated by patients 2 and 6.

All biopsies but one were performed while gross haematuria was still present, 3–25 days after its beginning (mean  $\pm$  SD =  $12.5 \pm 10$ ). The renal biopsy of patient 3 was performed 4 days after the end of the gross haematuria. After the histological and immunohistological findings, IgA nephritis was diagnosed in three patients (two primary, one due to Schönlein–Henoch purpura), pauci-immune focal necrotizing glomerulonephritis in two patients (necrotizing lesions in 17 and 7% of glomeruli), and acute postinfectious glomerulonephritis in another two patients (Table 2). Focal necrotizing glomerular lesions were also found in patients 4 and 5 (40 and 11% of glomeruli). Non-circumferential cellular crescents were observed in four biopsies, involving 4–33% of glomeruli. ATN was present in all biopsies (Figure 1), with scores ranging from 4 to 9. In all biopsies, erythrocyte casts (+ to + + +) and erythrocyte phagocytosis (+ to + +) were found, as well as interstitial red cell extravasation (+ to + + +) (Figure 2) and inflammatory cell infiltrates (+ to + +). Interstitial oedema was present in all but one case (+ to + +) (patient 2). Haemosiderin was found within the cytoplasm of the tubular cells in all biopsies (focal in patients 1, 2, 3, 5; diffuse in the other three) (Figure 3), while it was seen

Table 1. Clinical features

Patient	Sex	Age	Gross Hematuria (days)	Urinary protein (g/day)	Serum albumin (g/l)	Plasma creatinine(mg/dl)			Full recovery (*)
						Basal	Peak	Discharge(*)	
1	M	42	27	3.0	35	1.1	7.1	2.1 (22)	11 mo(**)
2	M	31	9	0.8	39	NA	12(D)	3.3 (26)	90
3	M	16	4	0	46	0.8	1.3	1.1 (12)	60
4	M	85	18	0.3	35	0.9	4.2	3.7 (9)	90
5	M	63	24	0.5	35	1.1	6.8	1.3 (22)	58
6	M	50	40	2.1	31	1.0	3.4	2.5 (16)	65 (§)
7	M	69	34	0.4	43	1.2	10.6	6.0 (10)	60 (§§)

Abbreviations: NA, not available; D, dialysis; mo, months; (\*) days after peak plasma creatinine; (\*\*) Several episodes of gross hematuria after discharge; (§) Pl creat 1.3 mg/dl, but patient lost to further follow-up; (§§) plasma creatinine 2.5 mg/dl at last check.

Table 2. Histological findings

Patient	Glomerular pathology	Diagnosis	Glomeruli number(*)	Crescents (%)	ATN (score)	Erythrocyte		Phagocytosis		Interstitial		Extravasation		Infiltrates	Vascular sclerosis(**)
						Casts				Oedema					
1	LM: Mesangial proliferative IF: IgA-C3	IgA-N	14(36)	11	5	+		++		++		+		+	+
2	LM: Focal necrotizing IF: C3	Necrotizing pauci-immune	12(0)	0	4	+++		++		0		++		±	0
3	LM: Mesangial proliferative IF: IgA-C3	Schönlein-Henoch-N	25(0)	4	9	+		+		+		+		±	0
4	LM: Exudative + necrotizing IF: C3-Fibr§	Acute post-infectious	16(6)	0	3	++		+		+		+		++	+
5	LM: Focal necrotizing IF: IgA-C3	IgA-N	14(14)	20	6	++		+		+		+		+	0
6	LM: Mesangial proliferative IF: C3	Acute post-infectious	10(0)	0	6	++		+		+		+		+	+
7	LM: Focal necrotizing IF: negative	Necrotizing pauci-immune	9(10)	33	4	+		+		+		+++		+	+

Abbreviations. ATN, acute tubular necrosis; LM, light microscopy; IF, immunofluorescence microscopy; N, nephritis; \* percentage of globally sclerotic glomeruli; \*\* arteriolar and/or arterial sclerosis; § fibrin(ogen) in the necrotizing areas of the glomerular tufts.

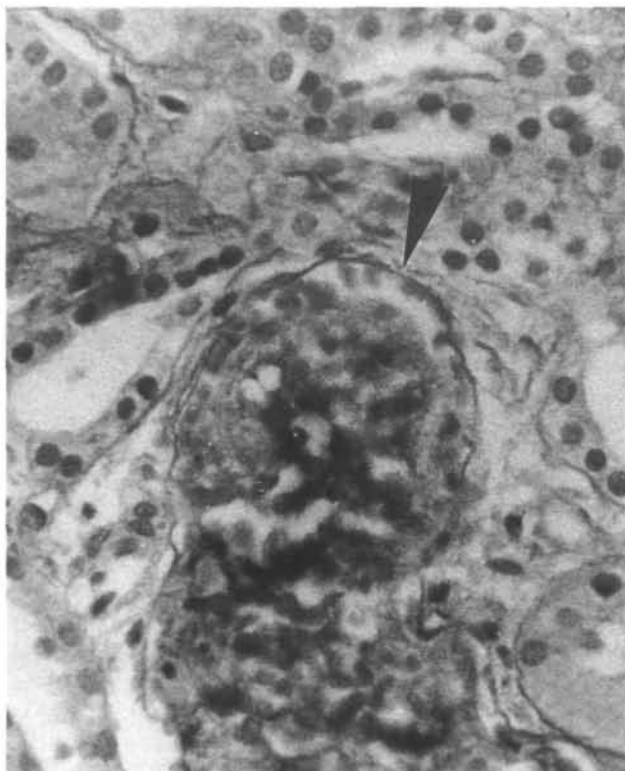


Fig. 1. Denuded basal membranes (arrow) of a tubule the lumen of which is filled with erythrocytes (patient 2, AFOG stain, original magnification 400 $\times$ ).

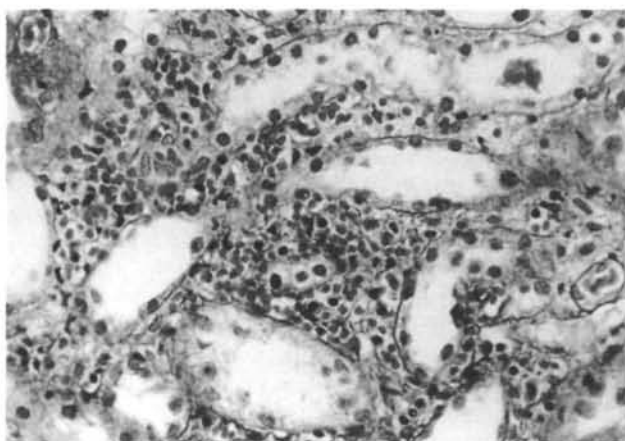


Fig. 2. Severe erythrocyte extravasation into the interstitium (patient 7, AFOG stain, 400 $\times$ ).

within the interstitium in only two cases (patients 6 and 7). Mild arterial sclerosis was present in four biopsies (patients 1, 4, 6, 7). Electron-microscopy studies (available only for patients 3, 6, and 7) revealed non-specific tubular damage, plus intratubular erythrocytes in different phases of dissolution. There was also evidence of erythrocyte uptake by the tubular cells (Figure 4), the cytoplasm of which contained increased amounts of lysosomes. All these lesions were unevenly distributed.

There was no close correlation between ATN score

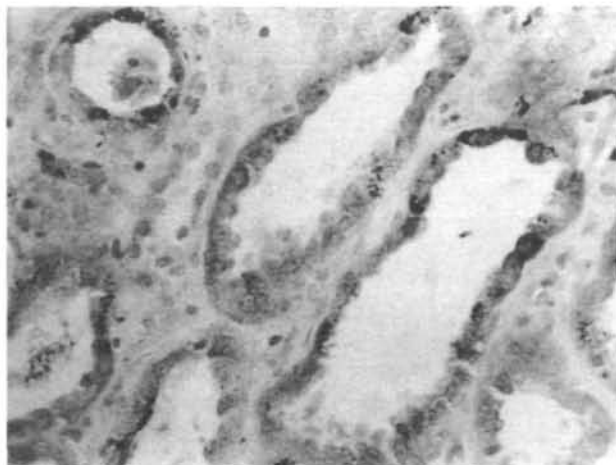


Fig. 3. Haemosiderin (black granules) in the cytoplasm of the tubular cells (patient 6, Perl's Prussian blue stain, 500 $\times$ ).

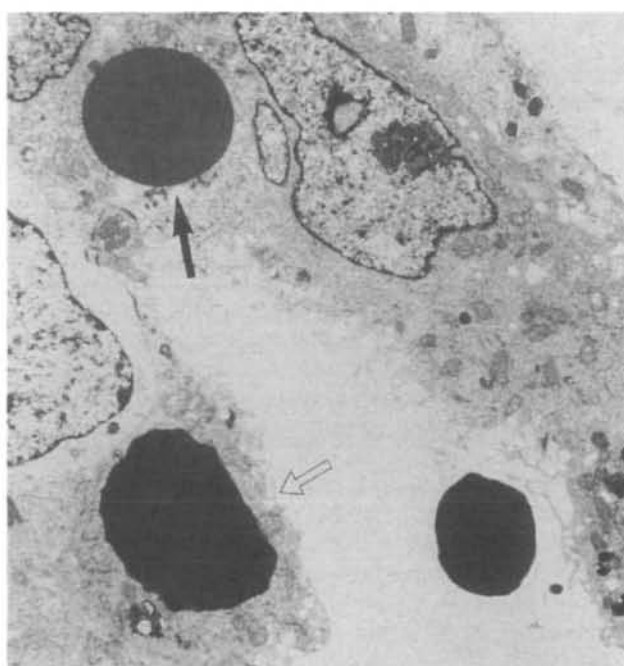


Fig. 4. Erythrocytes (arrows) within the cytoplasm of the tubular cells by electron-microscopy (patient 3, 8500 $\times$ ).

and the other histological parameters, as exemplified best by the biopsies of patients 2 and 3. Nor was the ATN score correlated with the duration of gross haematuria or with peak plasma creatinine levels. The lack of correlation could also be observed in plot of the two clinical parameters against the amount of erythrocyte casts. Patients with the necrotizing lesion had, on the average, higher peak plasma creatinine levels than the patients without ( $8.4 \pm 3.5$  versus  $3.9 \pm 2.9$  mg/dl).

Retrodiffusion of THp into Bowman's space was never found in any biopsy (Table 3), THp being present only in the cytoplasm of the distal tubules (6 of 7 biopsies) and in the intratubular casts. There was no extravasation of THp into the interstitium.

**Table 3.** Results of the immunofluorescence study with the antiserum to Tamm-Horsfall protein

Patient	Tamm-Horsfall protein		
	Bowman's space	Tubular cells	Intratubular casts
1	0/6	MF (+)	Many (+ + +)
2	0/9	MF (+ +)	Many (+ + +)
3	0/18	MF (+ +)	Few (+ + +)
4	0/12	MF (+ +)	Several (+ + +)
5	0/6	O	Few (+ +)
6	0/1	F (+)	Few (+ +)
7	0/3	MF (+)	Several (+ + +)

Abbreviations: MF, multifocal; F, focal; In parentheses, the intensity of the stain.

## Discussion

Acute renal failure from gross haematuria in patients with glomerulonephritis was first reported by Kincaid-Smith *et al.* [1,2], who demonstrated that the renal dysfunction was due to tubular necrosis which came along with intratubular erythrocyte casts, red-cell phagocytosis by tubular cells, and extensive interstitial oedema, rather than to the glomerular changes. Subsequently, Praga *et al.* [3], prospectively studied 29 episodes of gross haematuria in 21 patients with Berger's disease. Interestingly they found that acute renal failure did not occur in all patients, and that acute renal failure was significantly correlated with a longer duration of gross haematuria, higher amounts of intratubular erythrocyte casts, and a more extensive tubular necrosis. The severity and the duration of acute renal failure varied from patient to patient, but in all cases spontaneous and complete recovery of renal function was seen. Further reports described other similar cases [4–7], some of whom required temporary dialysis before going into remission. All patients but one [8] had IgA nephropathy. Of interest, also Delclaux *et al.* [7] found that not all patients with gross haematuria developed acute renal failure.

The patients described in this paper are similar to those reported so far in several respects. However, they also have several distinguishing clinical and pathological features. The interval of time before return to normal renal function was longer, on the average, than in the previous reports [1–7]. For case 1 the cause of the slow recovery of the renal function was probably the occurrence of additional episodes of gross haematuria in the months after discharge, even though no renal function tests were done when they occurred. Although the tubular damage was the most prominent finding in the renal biopsies of our patients, we cannot exclude that the glomerular lesions may have played a role in determining acute renal failure and/or in delaying renal function recovery. In fact four patients had a focal necrotizing lesion, which was not described in the previous series, and three of them also had globally sclerotic glomeruli. That this may partly

account for the acute renal failure is also supported by the finding that these patients had, on average, higher peak plasma creatinine levels than the patients without fibrinoid necrosis in the glomerular tufts. For patients with the necrotizing lesion, a course of corticosteroids may be justified to obtain or accelerate the repair of the glomerular damage, and therefore to stop the glomerular bleeding, which in turn is responsible for the tubular damage. Some of our patients had only mild renal vascular sclerosis and none had nephrotic syndrome. Thus we can reasonably exclude that vascular factors or other mechanisms involved in the acute renal failure seen in nephrotic patients [21] were operating in our cases.

Four patients in our series did not have IgA nephropathy, which instead was invariably present in the patients reported by others [1–7]. It is possible, however, that the other investigators deliberately chose to study IgA nephropathy, which is the glomerular disease most commonly associated with gross haematuria [22]. From our findings one can infer that acute renal failure from gross haematuria can be found in all haematuric glomerulonephritides, especially when they are accompanied by glomerular necrotizing lesions.

At variance with the findings of Praga *et al.* [3], but in agreement with those of Delclaux *et al.* [7], we did not find a close correlation between the duration of the gross haematuria and the severity of the renal insufficiency. Interstitial changes were always present in our patients, as in most of the previous series [1,5,6,7].

In spite of the fact that there were intratubular casts in all our biopsies, we were unable to observe retro-diffusion of THp into the glomerular Bowman's space, which has been observed in several other conditions such as obstructive uropathy [13–15], myeloma cast nephropathy [16,17], acute renal failure after acetazolamide intake [18], or in glomerular diseases associated with tubulointerstitial damage [12]. Since the retro-diffusion of THp into Bowman's space is considered to be a sign of intratubular obstruction, its absence in our patients suggests that this mechanism was not involved in the acute renal failure from gross haematuria. This is at variance with a previous hypothesis [1,9]. As an alternative explanation, it has been hypothesized that the tubular absorption of haemoglobin or other erythrocyte-derived substances results in tubular damage [1,3], and this has been demonstrated in animals [23,24]. Whether these acute tubulointerstitial lesions, especially when repeated, may lead to chronic renal insufficiency in the long term is still unclear. The available data would suggest that these patients do not have a worse outcome than patients without tubular lesions [7]. However, longer periods of observation and more patients are necessary to draw firm conclusions.

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### Editor's note

Please see also Editorial Comment by S. N. Heyman and M. Brezis (pp. 591–593 in this issue).

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